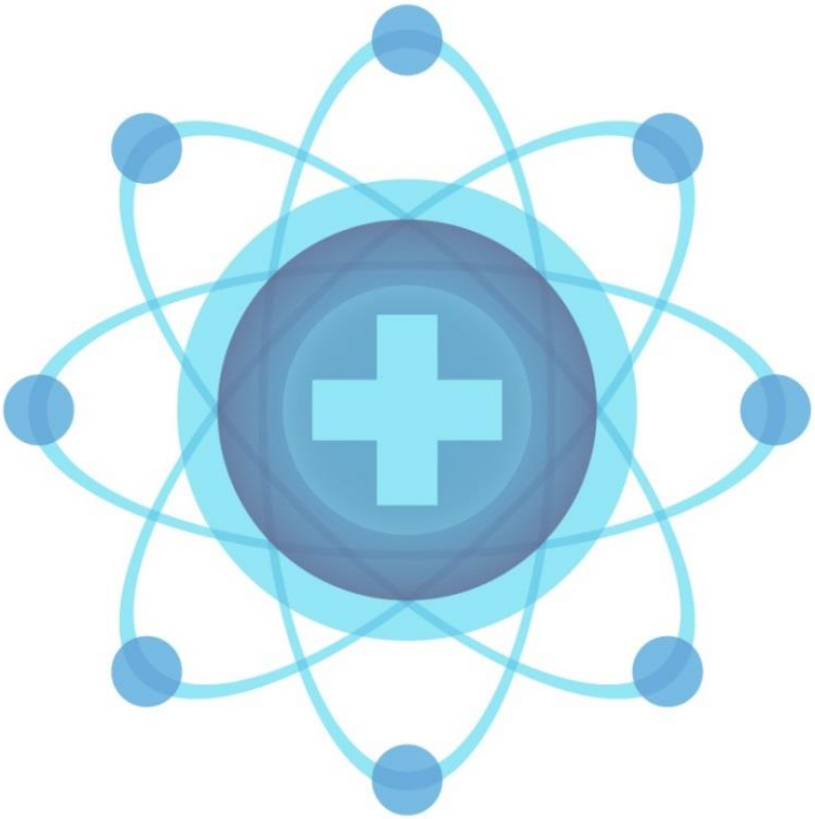

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FEATURES OF THE ILE462VAL ALLELIC POLYMORPHISM IN THE CYP1A1 GENE AMONG PATIENTS WITH CONGENITAL DEFECTS OF THE MAXILLOFACIAL REGION

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Abstract: The features of the polymorphism of the CYP1A1 gene (Ile462Val) among patients with HPVLO and healthy people in Uzbekistan were studied. The polymorphism of the CYP1A1 gene (Ile462Val) was assessed by analyzing DNA samples by setting the polymerase chain reaction (PCR) in Real Time mode .

Ile462Val polymorphism in the CYP1A1 gene among the studied groups of patients with HPVLO showed that the functionally unfavorable minor allelic variant G and the variant of the G / G genotype occur with a relatively high frequency, exceeding their values in the group of healthy individuals. More frequent carriage of these variants may indicate a trend towards an increased risk of developing an isolated cleft palate (Q 35; for the allele G - χ^2 =1.8; P=0.2 and genotype G / G - χ^2 \u003d 2.7; P=0.1) and lips (Q 36; for allele G - χ^2 =3.4; P=0.1 and genotype G / G χ^2 \u003d 1.4; P=0.3), which means that the studied Ile462Val polymorphism in the CYP1A1 gene may have a certain contribution to the mechanisms of the formation of these pathologies in Uzbekistan.

Keywords: HPVLO, isolated cleft palate, isolated cleft lip, combined cleft palate and lip, polymorphism CYP1A1 gene (Ile462Val) , allele, frequency, genotype, proportion of carriage, mechanism of development.

Relevance. Congenital malformations of the maxillary region (HML) are a group of diseases resulting from disturbances in the processes of regulation of embryogenesis [14]. To date , the etiological and pathogenetic mechanisms of HPVLO development remain poorly understood [9]. However, due to the continuous successful development and introduction of molecular genetic technologies into medicine in recent years, the contribution of genetic components to the mechanisms of the onset of HPVLO is now recognized [11,12,13].

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Today it is known that in the occurrence of HPVLO, as well as other human congenital malformations, an important role belongs to the system of biotransformation of xenobiotics [8,15,16], which performs complex processes of detoxification and removal of various environmental substances in the body, which have a negative impact on the stages fetal development, i.e. embryogenesis [3]. In particular, it should be noted that cytochrome P450 CYP1A1 takes part in the first phase of monooxygenase activation of the chemicals of this process, which results in the formation of reactive metabolites that have a toxic effect [6,7,10]. As a result of the replacement of isoleucine for valine in position 462 of this gene, enzymatic activity increases, leading to the accumulation of highly reactive intermediates in the cell, which increase the risk of changes in DNA through emerging mutations, initiating the onset of various diseases [1,2] , including HPVLO [4]. ,5].

Material and Methods: This study was conducted with the participation of 105 children aged 6.5±1.8 years with congenital malformations of the maxillofacial region. According to the ICD, 10 out of 105 children (I main group) have 35 isolated cleft palate (II group with Q 35), 33 have isolated cleft lip (III group with Q 36) and 37 have combined cleft lip and palate (group IV with Q 37). All patients were observed in the clinic of the Tashkent State Dental Institute (Tashkent) in the period from 2019 to 2022. The control group (V -th group) consisted of 103 healthy individuals with no history of congenital malformations, corresponding in sex and age with the examined main group of children with HPVLO.

In this study, all examined individuals underwent molecular genetic studies to study the features of the polymorphic variant of the gene CYP 1 A 1 (Ile 462 Val). Detection of a polymorphic gene variant CYP1A1 (Ile462Val) was carried out by SNP-PCR in Real Time mode on a programmable thermal cycler " Rotor Gene Q , (Quagen , Germany), using the test systems of the Litekh company (Russia), according to the manufacturer's instructions.

Statistical analysis of the results was carried out using the statistical software package OpenEpi 2009, Version 9.2. Comparative analysis of allele frequencies and genotypes of gene polymorphism CYP1A1 (Ile462Val) between the studied samples was carried out using the χ^2 test and Fisher's exact test. Differences were assessed as statistically significant at $P \leq 0.05$. In our studies, the frequency distribution of the genotype variants of the studied polymorphic CYP1A1 gene (Ile462Val) corresponded to the Hardy-Weinberg equilibrium (HWE) ($p>0.05$).

Results and discussion. Analysis of the results of the study on the assessment of occurrence of the Ile462Val allelic polymorphism in the CYP1A1 gene among patients of the main group with HPVLO (n =105) made it possible to determine the prevalence rates of the major (A) and minor alleles (G), which were 76.2% (n =160) and 23.6% (n =50). The frequencies of similar ones in the healthy group (n = 103) differed somewhat from those in the main HPVLO group, namely, for the major allele A, it was 83.0% (n = 171), and for the minor allele G , 17.0% (n = 35). The data obtained show a lower frequency of occurrence of the major functionally favorable allele A and, accordingly, a higher frequency of occurrence of the minor functionally unfavorable allele G among the examined main group with HPVLO. In

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addition to these facts, similar dynamics was observed in the frequencies of occurrence of all variants of the genotypes of the Ile462Val polymorphism in the CYP1A1 gene. So, if in the main group of patients with HPVLO the wild A/A genotype was found in 61.0% (n =64), and the heterozygous variant of the A/ G genotype and the homozygous mutant G / G variant in 30.4% (n =32) and 8.6% (n = 9) of the examined, then among healthy people their frequencies were recorded in 69.9% (n = 72), 26.2% (n = 27) and 3.9% (n = 4) cases (Table 1).

Table 1

Distribution of frequencies of alleles and genotypes of polymorphism Ile 462 Val in the CYP 1 A 1 gene in HPVLO patients and healthy controls

No.	Group	Allele frequency				Frequency distribution of genotypes					
		A		G		A/A		A/G		G/G	
		n	%	n	%	n	%	n	%	n	%
I	Main HPVLO group, n=105	160	76.2	fifty	23.8	64	61.0	32	30.4	9	8.6
II	Q35 (cleft palate) , n=35	53	75.7	17	24.3	22	62.9	9	25.7	four	11.4
III	Q36 (cleft lip) , n=33	48	72.7	eighteen	27.3	eighteen	54.6	12	36.4	3	9.0
IV	Q37 (cleft palate and lip) , n=37	59	79.7	fifteen	20.3	24	64.9	eleven	29.7	2	5.4
V	Control group , n=103	171	83.0	35	17.0	72	69.9	27	26.2	four	3.9

These results show that the most pronounced differences are visualized in the frequencies of occurrence of the minor allele G and the mutant genotype G / G , the proportion of which exceeds in the main group of those examined with HPVLO. It is possible that these variants of the Ile462Val polymorphism in the CYP1A1 gene may have a special contribution to the formation of HPVLO.

In addition to analyzing the prevalence of allelic and genotypic variants of the Ile462Val polymorphism in the CYP1A1 gene in the main group and control groups, they were assessed among patients depending on the nosology. In particular, among

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those examined with Q 35 (n = 35), alleles A (75.7%) and G (24.3%) had the closest values to those in the main group (76.2% and 23.8%, respectively). Meanwhile, among those examined with Q 36 (n = 33) they were detected in 72.7% and 27.3% of cases, and in the group Q 37 (n = 37) in 79.7% and 20.3% of the examined. According to the results obtained, it is obvious that the maximum frequency of the minor allele G was established in the group of patients with Q36, and the minimum frequency was found in Q37. At the same time, the dynamics of genotypic frequencies among these groups has a high occurrence of the major genotype A / A in the group of patients with Q37 (64.9%), then in descending order in 62.9% of cases this genotype was found in the group with Q35, and its lowest occurrence was found in group with Q36 (54.6%). However, in relation to the heterozygous genotype A / G , the dynamics had a completely different picture, namely, this variant was least often recorded in the group with Q35 (25.7%), the average values of its frequency were found in the group Q37 (29.7%), and the maximum values in the group with Q36 (36.4%). In addition to these features, for the G/G mutant genotype , the maximum occurrence was found in the group of patients with Q35 (11.4%), and the minimum in the group with Q37 (5.4%), while among those examined in the group with Q36, this variant of the genotype was found in 9.0% of patients.

Thus, the analysis of the occurrence of alleles and genotypes of the Ile462Val polymorphism in the CYP1A1 gene among the examined groups (Q35, Q36 and Q37) revealed differences in the share of their distribution, showing the highest frequency of carrying the heterozygous genotype A / G in the group of patients with Q36 and the homozygous unfavorable genotype G / G in the group examined with Q35, which may be due to their role in the formation of the corresponding pathologies. At the same time, to study their association with the onset of HPVLO, we conducted a deeper comparative statistical analysis of differences in the distribution of frequencies of the studied alleles and genotypes for the Ile462Val polymorphism in the CYP1A1 gene in all four groups of patients compared with healthy individuals.

Comparing the results of carriage of alleles and genotypes according to the studied polymorphic genetic variant between the main group with HPVLO and healthy ones, it was found that the functionally unfavorable G allele was 1.5 times more common among patients with HPVLO. At the same time, a pronounced trend was observed in relation to this (23.8%% vs. 17.0%; χ^2 \u003d 3.0; P \u003d 0.1; O R \u003d 1.5; 95% CI: 0.94-2.47-2.96), which indicates a trend towards increased risk formation of HPVLO in carriers of the G allele of the polymorphic CYP1A1 gene (Ile462Val).

Despite the fact that the heterozygous genotype A / G was detected 1.2 times more often among patients with HPVLO compared with healthy ones, the difference found was not statistically significant (30.5% vs. 26.2%; χ^2 <3.84; P = 0.5; O R = 1.2; 95%CI: 0.67-2.26) (Table 2) .

Table 2

Differences in the frequency of allelic and genotypic variants of the Ile 462 Val polymorphism in the CYP 1 A 1 gene in the main group of patients with HPVLO and healthy

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	R	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
A	160	76.2	171	83.0	3.0	0.1	0.9	0.61-1.38	0.7	0.4-1.06
G	fift y	23.8	35	17.0	3.0	0.1	1.1	0.64-1.87	1.5	0.94-2.47
A/A	64	61.0	72	69.9	1.8	0.2	0.9	0.52-1.48	0.7	0.38-1.19
A/G	32	30.5	27	26.2	0.5	0.5	1.2	0.66-2.04	1.2	0.67-2.26
G/G	9	8.6	four	3.9	2.0	0.2	2.2	1.03-4.73	2.3	0.71-7.56

At the same time, in the carriage of the G / G mutant genotype , as well as in the carriage of the G allele , a very pronounced tendency to its increase in comparison with the healthy group by 2.3 times was established (8.6% vs. 3.9%; χ^2 =2.0; P=0.2; O R =2.3; 95%CI: 0.71-7.56).

Comparing the frequency distribution of similar alleles and genotypes according to the Ile462Val polymorphism in the CYP1A1 gene in the group with Q 35 in relation to the control, the presence of a clear trend towards an increase in the occurrence of the minor allele G by 1.6 times (24.3% vs. 17.0%; χ^2 =1.8; P=0.2; O R = 1.6; 95% CI: 0.82-3.01). With this picture, the frequency of genotypes A / A (62.9% vs. 69.9%; χ^2 =0.6; P=0.5; O R =0.7; 95% CI: 0.33-1.63) and A / G (25.7% vs. 26.2%; χ^2 <3.84; P=0.97; O R =1.0; 95% CI: 0.41-2.34) did not differ significantly between the compared groups. Meanwhile, statistical analysis showed a strongly pronounced trend towards an increase in the proportion of the G / G mutant genotype . in the group with Q 35 3.2 times (11.4% vs. 3.9%; χ^2 =2.7; P=0.1; O R =3.2; 95% CI: 0.8-12.68) compared with that in the control group (Table 3) .

Table 3

Differences in the frequency of allelic and genotypic variants of the Ile 462 Val polymorphism in the CYP 1 A 1 gene in groups of patients with Q35 and healthy people

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	R	RR	95%CI	OR	95%CI
	Q35		Control group							
	n	%	n	%						
A	53	75.7	171	83.0	1.8	0.2	0.9	0.37-2.23	0.6	0.33-1.23
G	17	24.3	35	17.0	1.8	0.2	1.1	0.74-1.63	1.6	0.82-3.01
A/A	22	62.9	72	69.9	0.6	0.5	0.9	0.29-2.83	0.7	0.33-1.63
A/G	9	25.7	27	26.2	0.0	0.97	1.0	0.27-3.55	1.0	0.41-2.34
G/G	four	11.4	four	3.9	2.7	0.1	2.9	0.67-13	3.2	0.8-12.68

Therefore, the obtained results indicate the contribution of the minor allele G and the G / G genotype for the polymorphic variant of the CYP1A1 gene (Ile462Val) to the mechanisms of the formation of cleft palate (Q 35), increasing the risk of developing this defect by 1.6 and 3.2 times.

Even more significant results were obtained in a comparative analysis of differences in the carriage of alleles and genotypes of the polymorphic CYP1A1 gene (Ile462Val) in the group of patients with Q36 , in which, compared with the healthy group, there was a strongly pronounced tendency to increase the frequency of the functionally unfavorable G allele by 1.8 times (27.3% vs. 17.0%; χ^2 =3.4; P=0.1; O R =1.8; 95% CI: 0.96-3.5) . Moreover, in the studied group of patients, compared with the control, the frequencies of heterozygous A / G and homozygous minor G / G genotypes also showed a tendency to their increase by 1.6 (36.4 % vs. =1.4; P=0.3; O R =2.5; 95%CI: 0.55-11.18), respectively. The obtained results prove the participation of the G allele , as well as the A / G and G / G genotypes of the polymorphic CYP1A1 gene (Ile462Val) in the mechanisms of cleft lip formation (Q36), increasing the risk of developing the disease by 1.8; 1.6 and 2.5 times respectively (Table 4) .

Table 4

Differences in the frequency of allelic and genotypic variants of the Ile 462 Val polymorphism in the CYP 1 A 1 gene in groups of patients with Q36 and healthy people

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	R	RR	95%CI	OR	95%CI
	Q36		Control group							
	n	%	n	%						
A	48	72.7	171	83.0	3.4	0.1	0.9	0.36-2.12	0.5	0.29-1.04
G	eighteen	27.3	35	17.0	3.4	0.1	1.1	0.76-1.71	1.8	0.96-3.5
A/A	eighteen	54.5	72	69.9	2.6	0.2	0.8	0.25-2.46	0.5	0.23-1.15
A/G	12	36.4	27	26.2	1.3	0.3	1.4	0.42-4.53	1.6	0.7-3.69
G/G	3	9.1	four	3.9	1.4	0.3	2.3	0.39-3.96	2.5	0.55-11.18

However, analyzing the distribution of allele and genotype frequencies of the polymorphic CYP1A1 gene (Ile462Val) in the group of patients with Q37, we did not reveal any differences with statistically significant significance. So, although in the group of patients with Q 37 the frequency of the allele G and exceeded the similar one in the control by 1.2 times (20.3% vs. 17.0%; χ 2 = $^{0.4}$; P=0.6; O R =1.2;) , and the frequencies ^{of} genotypes A / G and G / G were higher in 1.2 (29.7 % vs. % vs. 3.9%; χ^2 =0.2; P=0.7; O R =1.4; 95% CI: 0.25-8.0), respectively, similar in the compared control group, yet the differences did not differ in their significance (Table 5) . This means that the data obtained prove the absence of the contribution of the studied alleles and genotypes of the polymorphic CYP1A1 gene (Ile462Val) in the mechanisms of the formation of the combined defect of cleft lip and palate (Q37), which is possibly associated with other mechanisms leading to the development of Q37 compared to the development of Q35 and Q36.

Table 5

Differences in the frequency of allelic and genotypic variants of the Ile 462 Val polymorphism in the CYP 1 A 1 gene in groups of patients with Q37 and healthy

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	R	RR	95%CI	OR	95%CI
	Q37		Control group							
	n	%	n	%						
A	59	79.7	171	83.0	0.4	0.6	1.0	0.38-2.45	0.8	0.41-1.58
G	fifteen	20.3	35	17.0	0.4	0.6	1.0	0.71-1.53	1.2	0.63-2.43
A/A	24	64.9	72	69.9	0.3	0.6	0.9	0.3-2.85	0.8	0.36-1.76
A/G	eleven	29.7	27	26.2	0.2	0.7	1.1	0.35-3.66	1.2	0.52-2.73
G/G	2	5.4	four	3.9	0.2	0.7	1.4	0.14-13.7	1.4	0.25-8.0

After analyzing the degree of difference in the frequencies of distribution of alleles and genotypes polymorphic gene CYP1A1 (Ile462Val) in the groups of patients compared with the control further, it seemed interesting to us to conduct a comparative analysis of the characteristics of their carriage between the groups Q 35, Q 36 and Q 37. However, the identified differences between the studied groups did not reach the degree of reliability. Thus, the differences in the frequencies of the allelic variant G of the Ile462Val polymorphism in the CYP1A1 gene between the groups of patients with Q35 and Q36 were less than one (24.3% versus 27.3%; χ^2 =0.2; P=0.7; O R =0.9 ; 1.85). A similar difference, which did not reach one, was also found for the A / G genotype variant . (25.7% vs 36.4%; χ^2 =0.9; P=0.4; O R =0.6; 95% CI: 0.22-1.7). At the same time, although the variant of the G / G genotype in the group of patients with Q35 exceeded that among patients with Q36 by 1.3 times (11.4% vs. 9.1%; χ^2 =0.1; P=0.8; O R =1.3; 95% CI: 0.27-6.24), yet the difference was not statistically significant.

The absence of statistically significant differences between the studied groups of patients is associated with relatively close proportions of alleles and genotypes of the Ile462Val polymorphism in the CYP1A1 gene.

A similar study of the distribution of the Ile462Val polymorphism in the CYP1A1 gene between the Q35 and Q37 groups also showed no statistically significant differences in the carrier frequencies of the G allelic variant (24.3% vs. 20.3%; χ^2 =0.3; P=0.6; O R =1.3; 95% CI : 0.57-2.77) and genotype A/ G (25.7% vs 29.7%; χ^2 =0.1; P=0.8; O R =0.8; 95% CI: 0.29-2.3). With respect to the variant of the G / G genotype in the group of patients with Q35, although weak, there was still a tendency to increase it compared to that in the Q37 group by 3.3 times (11.4% vs. 5.4%; χ^2 =0.9; P=0.4; O R = 2.3; 95% CI: 0.4-12.7), which is probably due to the relatively small number of patients .

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Statistically significant differences in the distribution of alleles and genotypes of the Ile462Val polymorphism in the CYP1A1 gene between the Q36 and Q37 groups were also not found: for the G allele (27.3 % vs. 0.67-3.22); for genotypes A / G (36.4% vs 29.7%; χ^2 =0.6; P=1.2; O R =1.4; 95% CI: 0.5-3.67) and G / G (9.1% vs 5.4%; χ^2 =0.4; P=0.6; O R =1.7; 95% CI: 0.28-11.0).

Conclusion _ Thus, analyzing the results of studying the distribution features in the frequency of occurrence of alleles and genotypes of the Ile462Val polymorphism in the CYP1A1 gene among the studied groups of patients with HPVLO, it was found that the functionally unfavorable minor allelic variant G and the variant of the G / G genotype occur with a relatively high frequency exceeding their values in a group of healthy individuals. More frequent carriage of these variants may indicate a trend towards an increased risk of developing an isolated cleft palate (Q 35; for the allele G - χ^2 =1.8; P=0.2 and genotype G / G - χ^2 \u003d 2.7; P=0.1) and lips (Q 36; for allele G - χ^2 =3.4; P=0.1 and genotype G / G χ^2 \u003d 1.4; P=0.3), which means that the studied Ile462Val polymorphism in the CYP1A1 gene may have a certain contribution to the mechanisms of the formation of these pathologies in Uzbekistan.

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